Anesthesiology 2007; 107:6–7

Multisystem Organ Failure

Predicting the Future

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MULTISYSTEM organ failure is a devastating condition most often associated with severe sepsis, but which can occur with other conditions such as trauma, pancreatitis, and burns. All of these conditions likely share a common pathway for the development of multiple system organ failure: diffuse activation of endothelium by proinflammatory cytokines, leukocytes, and other proteins. Activated endothelium becomes prothrombotic in these conditions, leading to formation of microvascular thrombosis. In addition, fibrinolysis is inhibited, resulting in buildup of fibrin thrombus, which itself is proinflammatory. Normal antithrombotic mechanisms such as protein S, protein C, and antithrombin III are inhibited or overwhelmed. When microvascular thrombosis occurs, capillary beds in organs such as the lung and kidney become injured, and neutrophils bind and release proinflammatory cytokines and proteases, resulting in multisystem organ failure.[1,2] In this issue of ANESTHESIOLOGY, Brunkhorst *et al.*[3] correlate the plasma concentration of protein C, a critical profibrinolytic and antiinflammatory protein, with outcome in 312 consecutive patients admitted to a surgical intensive care unit. Although protein C has been well studied in patients with severe sepsis, this is the first study of serial protein C concentrations in a heterogeneous population of surgical intensive care unit patients.

Our understanding of the pathophysiology of multisystem organ failure comes from basic and clinical studies of sepsis. The pathophysiology of sepsis is complex, and includes abnormalities in immune, inflammatory, and hemostatic pathways. The coagulation and inflammatory pathways are closely linked, and the inflammatory state associated with sepsis results in a procoagulant response in the host.[4] There are a number of counterregulatory molecules that function to counteract the procoagulant state seen in sepsis. For example, antithrombin III is a hepatically synthesized glycoprotein that functions as an inhibitor of the intrinsic, extrinsic, and common coagulation pathways. Antithrombin III binds to endothelial cell membranes, resulting in an increase in prostacyclin synthesis. This prostacyclin inhibits platelet aggregation and neutrophil binding. Protein C is a member of the vitamin K–dependent family of coagulation proteins, which circulates as an inactive zymogen. Under conditions of thrombotic and inflammatory stress, it binds with endothelial surface thrombomodulin and is cleaved to form activated protein C. Activated protein C functions as a feedback inhibitor of thrombin, inhibits leukocyte adhesion to endothelial cells, and prevents further thrombus formation by binding factor Va and VIIIa. In addition, activated protein C inactivates plasminogen activator inhibitor 1 and prevents activation of thrombin activatable fibrinolysis inhibitor; the net result of these actions is facilitation of fibrinolysis and removal of fibrin clot from the microcirculation. Dissolution of this fibrin thrombus removes the inflammatory stimulus. Tissue factor pathway inhibitor is an endogenous protease inhibitor, which inhibits factor Xa directly, and secondarily inhibits the factor VIIIa–tissue factor complex. All three of these compounds have been synthesized for therapeutic use.

Recognition of the aforementioned coagulation abnormalities in sepsis has led to efforts to test the efficacy of these counterregulatory molecules in clinical trials. In 1997, Smith *et al.*[5] used protein C concentrate to treat 12 children with meningococcemia-induced purpura fulminans. All the children survived (expected mortality 30–40%), and there were fewer amputations (a common complication of purpura fulminans). This study, and the recognition that patients with severe sepsis exhibit protein C deficiency, led to a prospective, randomized trial of recombinant human activated protein C in patients with severe sepsis.[6,7] This trial demonstrated a 6.5% reduction in the risk of death in 871 patients with severe sepsis treated with a 4-day course of human recombinant activated protein C (Xigris®; Eli Lilly, Indianapolis, IN). This trial has proven controversial, with concerns raised regarding the actual efficacy and bleeding risk, but recombinant

◆ This Editorial View accompanies the following article: Brunkhorst K, Sakr Y, Hagel S, Reinhart K: Protein C concentrations correlate with organ dysfunction and predict outcome independent of the presence of sepsis. ANESTHESIOLOGY 2007; 107:15–23.

Accepted for publication March 21, 2007. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

human activated protein C remains the only US Food and Drug Administration–approved treatment for severe sepsis.[8] Two other potential pharmacotherapies focusing on treating the procoagulant state in sepsis, antithrombin III and tissue factor pathway inhibitor, did not show efficacy in randomized, prospective trials, and both agents demonstrated increased risk of bleeding.[9,10] Neither agent was approved for human use.

Despite these mixed results in clinical trials, intensivists remain hopeful for a "silver bullet" for multiple system organ failure. Brunkhorst *et al.*[3] report an observational study of 312 consecutive patients admitted to a surgical intensive care unit. They measured daily plasma protein C concentrations, correlating them with physiology-based severity of illness measures including the Acute Physiology and Chronic Health Examination II, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment Score, and McCabe. All categories of patients had decreasing protein C concentrations over the course of their intensive care unit stay. However, the minimum protein C concentration was independently associated with mortality regardless of diagnosis. Patients with severe sepsis had the lowest concentrations of protein C. Interestingly, minimum protein C concentration had the same predictive power for mortality as did traditional severity of illness scoring systems such as Acute Physiology and Chronic Health Examination II and Simplified Acute Physiology Score.

Could a simple blood test of procoagulant activity replace more complex physiology-based prognostic systems? Matthay *et al.*[11] found that patients with acute respiratory distress syndrome had significantly lower plasma protein C levels when compared with controls. In addition, levels of endothelial protein C receptor were significantly different between patients with Simplified Acute Physiology II Scores less than and greater than 45. In another study, the same group found that protein C levels could differentiate survivors from nonsurvivors, duration of mechanical ventilation, number of organ system failures, and presence or absence of shock.[12] These findings suggest that perhaps the best determinant of severity of illness and survival are measures of inflammation, and secondarily procoagulant state. That is, physiology is determined by pathology, not *vice versa*.

Brunkhorst *et al.* should be congratulated for performing the largest study to date of protein C concentrations in critically ill patients. They illustrate the fact that procoagulant activity is important in clinical conditions other than severe sepsis, and that it is organ failure and not infection that determines protein C deficiency. It remains unclear whether targeting the protein C pathway with recombinant human activated protein C or other agents will improve outcomes in patients with multisystem organ failure independent of sepsis, but one could imagine that protein C concentration could be a useful predictor of both resuscitation efficacy and prognosis in this patient population. In the future, could we measure real-time plasma protein C levels, and treat protein C deficiency with recombinant human protein C? We await further studies of the coagulation pathway in the hopes of new therapies for this devastating syndrome.

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